



TITLE:

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The Synthesis of Alkaloids Using a Transition-Metal-Catalyzed Intramolecular Amination Reaction

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Abstract: Transition-metal catalyzed reactions have the potential to provide significant improvements to the syntheses of complex target molecules. These reactions can be used to achieve a variety of different atom-economical transformations and cascade reactions and therefore provide access to synthetic strategies that would otherwise be unavailable using classical organic chemistry. To exemplify the utility of the latest transition metal catalyzed reactions for the construction of important target structures, we have been involved in total synthesis of natural products bearing widely known chemical scaffolds. In this account, we report our recent studies on the use of a palladium-catalyzed cascade cyclization reaction and a gold(I)-catalyzed hydroamination reaction, for the construction of the core structures of alkaloids, as well as their application to total syntheses of lysergic acid, lysergol, isolysergol, and quinocarcin.

- 1 Introduction
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Key words: Total synthesis, palladium, gold, alkaloids, atom economy

1 Introduction

Making improvements to the step and atom economies of organic transformations is one of the most important requirements in modern organic chemistry.¹ Transition metal catalysts have had a significant impact on the facility with which organic chemists can access complex target structures by providing synthetic strategies for the construction of target molecule that would otherwise be difficult or even impossible to access using classical organic chemistry. To demonstrate the power of transition metal catalysis in organic chemistry, we have been working towards the synthesis of natural products using transition-metal-catalyzed cyclization reactions. A series of well-known chemical scaffolds were selected as the targets of our study including those of the ergot alkaloids (e.g., lysergic acid, lysergol, and isolysergol) and the tetrahydroisoquinoline alkaloids

(e.g., quinocarcin). Although several efficient total syntheses of these natural products have already been reported (for details, see the introduction text of sections 2 and 3), our current approach represents a unique strategy that sometimes provide improvements in the step and atom economies of the syntheses of these compounds, as well as providing a platform for the synthesis of other complex natural products. Herein, we describe our recent work towards the synthesis of ergot alkaloids using a palladium-catalyzed cascade cyclization of allenes, as well as a gold(I)-catalyzed hydroamination for the synthesis of tetrahydroisoquinoline alkaloids.

2 Ergot Alkaloid Synthesis

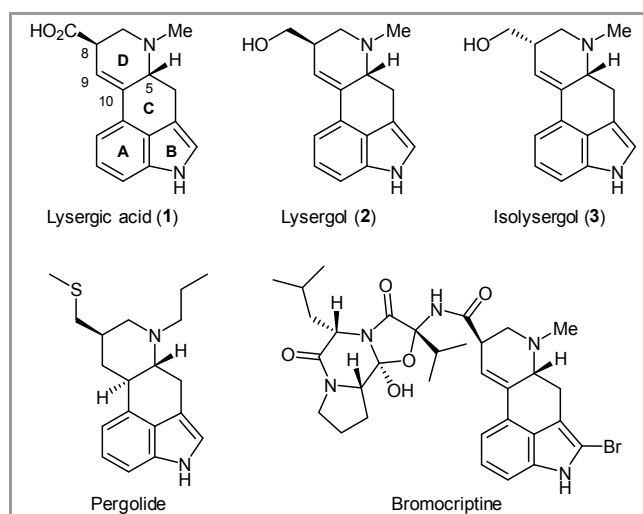


Figure 1 Indole alkaloids of the ergot family and their synthetic derivatives.

The ergot family of alkaloids consists of several pharmacologically important fused indoles, including lysergic acid (1), lysergol (2), and isolysergol (3) (Figure 1). Compounds belonging to this particular family are produced by the fungus *Claviceps purpurea*, which grows parasitically on rye and other grains,² and have been reported to possess a variety of different biological activities. For example, pergolide and bromocriptine, which are synthetic derivatives of the ergot alkaloids, are clinically used as anti-prolactin and anti-Parkinson's disease drugs, respectively.³ Lysergic acid diethylamide (LSD) is well known as a strong psychoactive agent. The characteristic

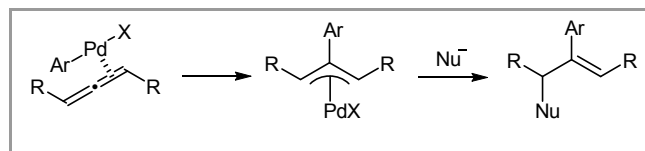
structural feature of these alkaloids is their tetracyclic fused indole, which contains a $\Delta^{9,10}$ -double bond and chiral centers at the C5 and C8 positions.

Ergot alkaloids, especially lysergic acid, have been the target of many synthetic studies because of their biological importance as well as their structural complexity. The first total synthesis of racemic lysergic acid was accomplished by Woodward in 1956.^{4a} Several racemic syntheses of ergot alkaloids have subsequently been reported,^{4,5} with most of the strategies involving the stepwise and linear construction of the C/D ring system. One important exception, however, is the strategy described by Oppolzer,^{4d} which involved the simultaneous construction of the C/D rings through an intramolecular imino-Diels–Alder reaction. The asymmetric total synthesis of lysergic acid was first reported in 2004 by Szántay and coworkers,^{6a} which involved the resolution of a racemic tetracyclic intermediate using dibenzoyl-L-tartaric acid. In 2009, Fukuyama *et al.* reported the asymmetric synthesis of the methyl ester of lysergic acid using a Heck cyclization reaction^{6b} or palladium-catalyzed double-cyclization (*N*-arylation and Heck reaction).^{6c} More recently, Jia^{6e} reported the asymmetric total synthesis of lysergic acid using a RCM reaction as the key step. This particular report was published after our own report (*vide infra*).^{6d}

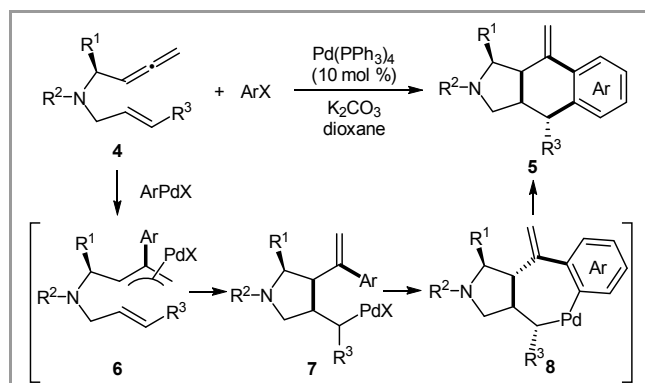
Based on our recent studies towards palladium-catalyzed cascade cyclization reactions, we designed a novel strategy for the construction of the core structure of ergot alkaloids that could be used for the asymmetric total synthesis of lysergic acid (**1**), lysergol (**2**), and isolysergol (**3**).

2.1 Construction of the Core Structure of the Ergot Alkaloids using a Palladium-Catalyzed Cascade Cyclization^{4j}

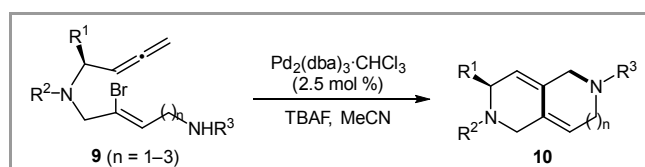
It is well known that arylpalladium halides generated *in situ* from the reaction of aryl halides with palladium(0), can regioselectively react with allenes to form η^3 -allylpalladium(II) intermediates (Scheme 1).^{7,8} In 2003, we reported the direct formation of the tricyclic isoindole derivatives **5** from allenes **4** using an alkene carbopalladation reaction followed by a direct arylation/C–H bond functionalization (**7** to **8**) (Scheme 2).⁹ The reaction of **4** with heterocyclic aryl halides provided direct access to the corresponding tri- and tetracyclic heteroaromatic products. More recently, we reported a fully intramolecular cascade cyclization reaction using amino allene derivatives,¹⁰ with similar results also being reported by some other groups.^{11,12} For example, the reaction of **9** under these conditions terminates with the nucleophilic attack of a protected amino group to afford **10** (Scheme 3).¹⁰



Scheme 1 General Scheme for Palladium-Catalyzed Reaction of Allenes with Aryl Halides and Nucleophiles

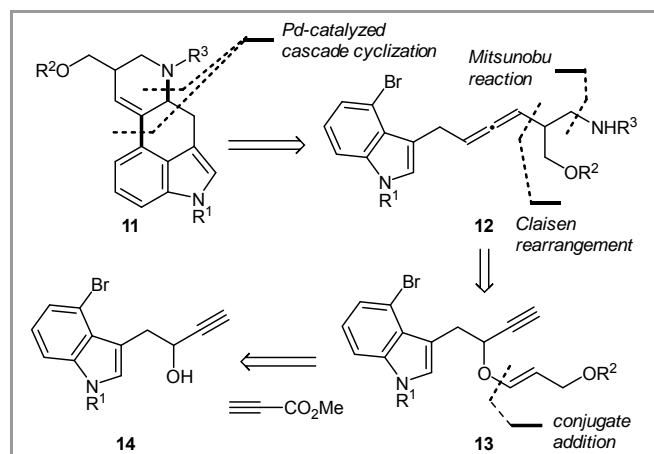


Scheme 2 Palladium-Catalyzed Cascade Cyclization of Allenene Derivatives with an Aryl Halide.



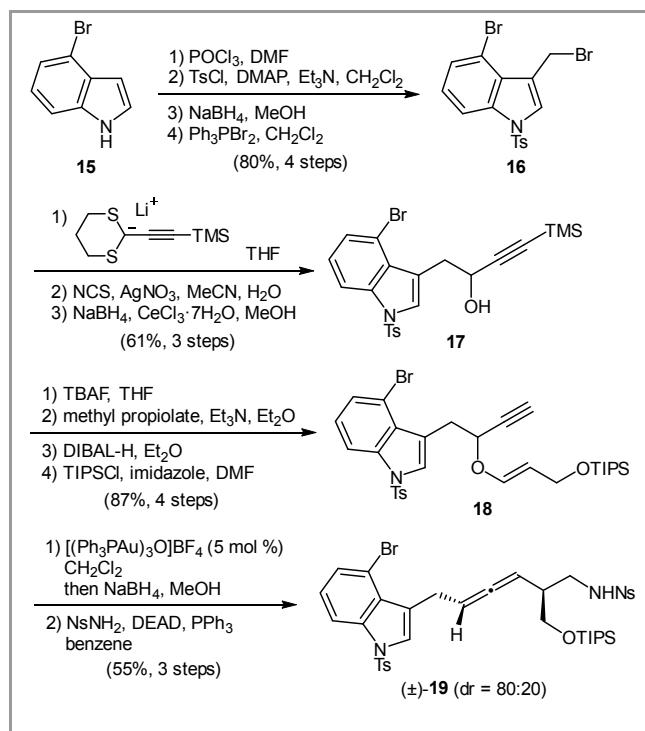
Scheme 3 Palladium-Catalyzed Fully Intramolecular Cascade Cyclization of Amino Allene Derivatives.

In light of this chemistry, it was envisaged that the palladium-catalyzed cascade cyclization of amino allenes **12** bearing a protected 4-bromoindol-3-yl group (Scheme 4) would provide direct access to tetracyclic indoles **11** bearing the core structure of the ergot alkaloids. The development of such a strategy for the construction of the desired 6,6-fused C/D ring system would be challenging, because the reaction of an internal allene bearing an aryl halide and amino group at both ends was unprecedented.^{10–12} The allene unit of **12** could be constructed via the Claisen rearrangement of the propargyl enol ether **13**, which could be readily obtained through the conjugate addition of propargyl alcohol **14** to methyl propiolate.



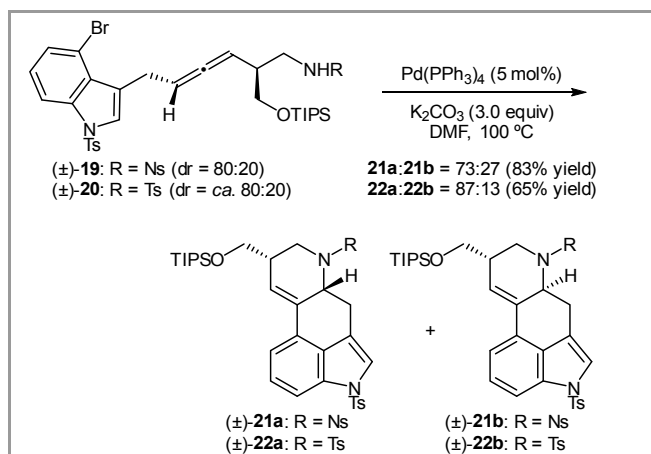
Scheme 4 Retrosynthetic Analysis of the Racemic Cyclization Precursor **12**.

Racemic allenic amide **19** was prepared as a model compound to evaluate the overall scope of our strategy for the construction of the core structure of ergot alkaloids (Scheme 5). Commercially available 4-bromoindole (**15**) was readily converted to the protected 3-(bromomethyl)indole (**16**) via the formylation of the indole at the 3-position, followed by sequential *N*-tosylation, reduction of the 3-formyl group, and the bromination of the resulting primary hydroxy group. The addition of lithiated 1,3-dithiane¹³ to **16**, followed by hydrolysis of the thiactal,¹⁴ and subsequent reduction of the resulting ketone gave racemic propargyl alcohol **17**. The propargyl vinyl ether **18** was then obtained via the conjugate addition of **17** to methyl propiolate,¹⁵ followed by sequential DIBAL reduction of the resulting enolate and TIPS protection of the resulting alcohol. The Claisen rearrangement of **18** under thermal conditions (*m*-xylene, 170°C) did not proceed as anticipated and gave the desired allenic alcohol (dr = *ca.* 33:67) in a low yield of only 38%. Pleasingly, however, the use of 5 mol% of the gold-oxo complex [(Ph₃PAu)₃O]BF₄¹⁶ gave the rearrangement product in 78% yield following the reduction of the aldehyde with NaBH₄ (dr = *ca.* 80:20, favoring the opposite diastereomer to the thermal conditions). A Mitsunobu reaction with NsNH₂ gave the allenic nosylamide derivative **19** as a mixture of diastereomers (dr = 80:20), which was progressed directly into the subsequent step without separation. The corresponding tosylamide derivative **20** (dr = *ca.* 80:20) (Scheme 6) was also prepared in a similar manner using TsNHFmoc in the Mitsunobu reaction.¹⁷



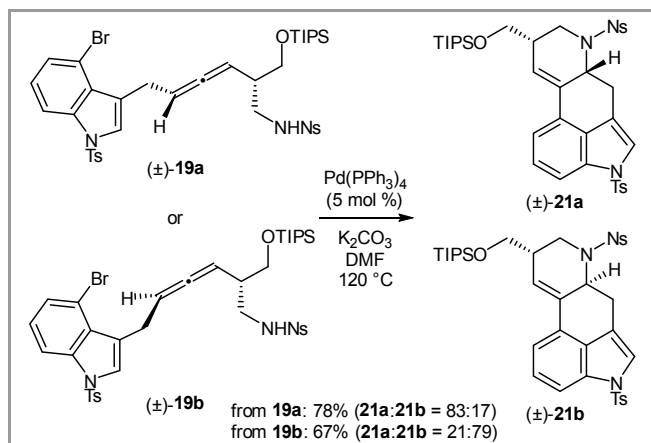
Scheme 5 Synthesis of the Racemic Cyclization Precursor **19** by a Gold-Catalyzed Claisen Rearrangement

We then proceeded to investigate the construction of the ergot alkaloid skeleton using the palladium-catalyzed cascade cyclization (Scheme 6). Among the different palladium catalysts [Pd(OAc)₂/PPh₃, PdCl₂(dppf), Pd(OAc)₂/P(*o*-tol)₃ and Pd(OAc)₂/*rac*-BINAP], bases (Na₂CO₃, Cs₂CO₃, and K₂CO₃), and solvents (DMF, DMSO, toluene, and dioxane) tested, a combination of 5 mol% of Pd(PPh₃)₄ with K₂CO₃ in DMF was found to be the most effective, and gave the desired tetracyclic indole **21** in 83% yield as a 73:27 stereoisomeric mixture. When the *N*-tosyl derivative **20** was subjected to the optimized reaction conditions, the desired product **22** was isolated in 65% yield with good diastereoselectivity (87:13). The decision was taken to use the tosylamide as the cyclization precursor for our asymmetric total syntheses in the current study because of the stereoselectivity and ease of deprotection that this group offered (Section 2.2).



Scheme 6 Construction of the Ergot Alkaloid Core Structure Using the Palladium-Catalyzed Cascade Cyclization

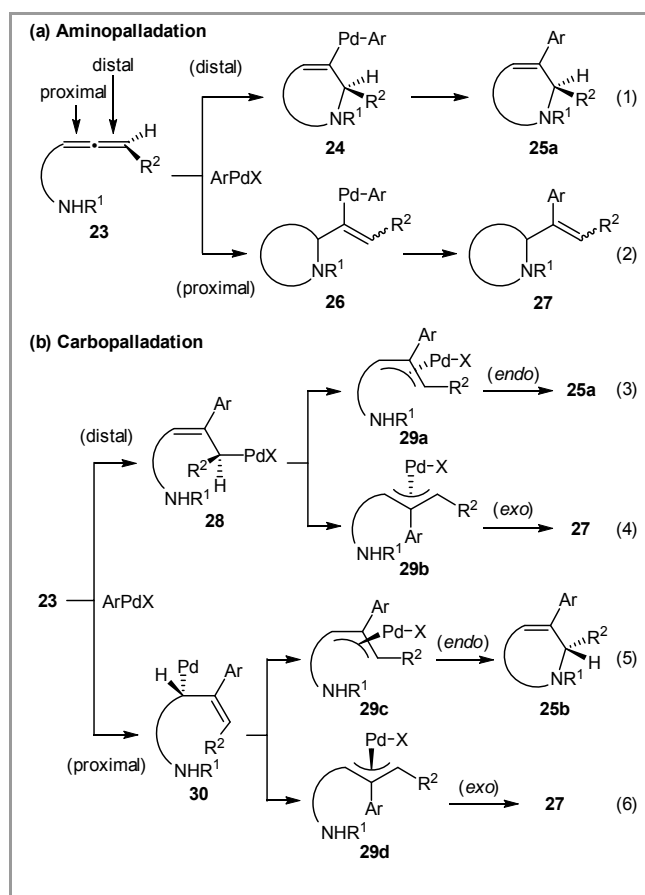
The different diastereomers of the allene were carefully separated by HPLC and subjected to the cascade cyclization conditions to develop a deeper understanding of the reaction mechanism (Scheme 7). The major isomer **19a** gave an 83:17 mixture of isomers in 78% yield, with **21a** being isolated as the major cyclized product, as anticipated. In contrast, the minor isomer **19b** gave the other diastereomer **21b** (**a:b** = 21:79) as the major product in a combined yield of 67% yield. These results can be understood in terms of the aminopalladation pathway, as discussed below.



Scheme 7 The Cascade Cyclization of Each Diastereomer

It can be difficult to predict the product distribution of the palladium-catalyzed cyclization of amino allenes with an aryl halide,¹⁸ because reactions of this type can proceed via the two competing major pathways, including (a) the aminopalladation¹⁹ and (b) carbopalladation²⁰ pathways (Scheme 8). In the aminopalladation pathway, the arylpalladium halide activates the distal double bond of the amino allene **23** from the least hindered side and promotes an *endo*-type cyclization (eq 1), with nitrogen heterocycle **25a** being formed stereospecifically via a reductive elimination step. The occurrence of an aminopalladation reaction at the proximal double

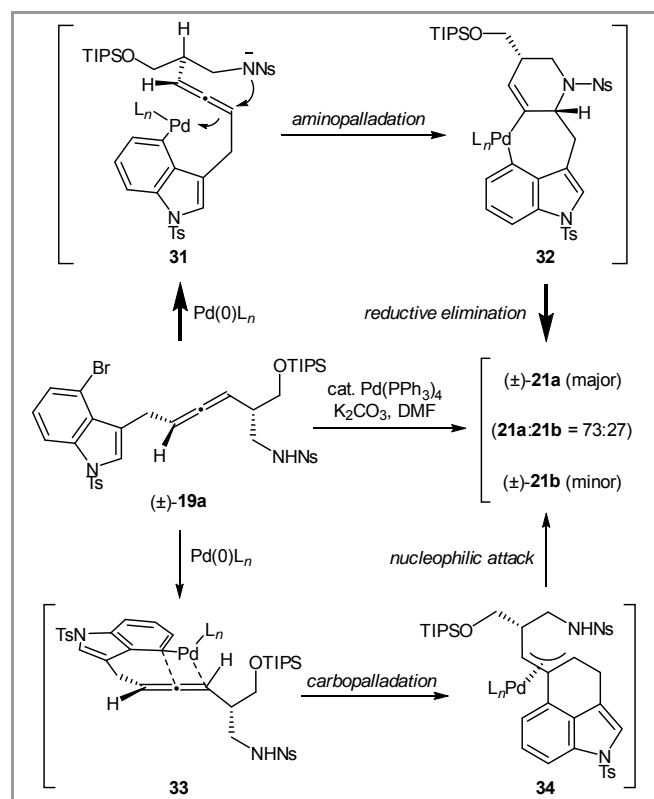
bond would give its regioisomer **27** (eq 2). In contrast, carbopalladation onto the distal double bond from the least hindered side of the double bond would give the η^1 -allylpalladium(II) intermediate **28**, which would lead to the η^3 -intermediates **29a** and **29b** through isomerization. Subsequent intramolecular *anti*-cyclization would then give the *endo*-cyclization product **25a** (eq 3) and/or the *exo*-cyclization product **27** (eq 4). These are the same products as those formed from the distal and proximal bond aminopalladation pathways (eqs 1 and 2). It is noteworthy that the cyclization product **25b**, formed through a carbopalladation at the proximal double bond followed by an *endo*-cyclization (eq 5), has the opposite configuration to the distal aminopalladation product **25a** (eq 1). The *exo*-type cyclization product **27** could also be formed from the η^3 -allylpalladium intermediates **29d** (eq 6), which makes it particularly difficult to predict the outcome of reactions of this type.



Scheme 8 General Reaction Pathways for the Palladium-Catalyzed Reaction of Amino Allenes with Arylpalladium Halides

In our case, aminopalladation at the distal double bond (as in eq 1 of Scheme 8 to form **25a**) adequately explains the formation of the major isomer **21a** from the amino allene **19a** (Scheme 9). Coordination of the indolylpalladium(II) to the allenic moiety would promote *anti*-attack of the sulfonamide group as shown in **31**. Aminopalladation from the favored

conformation would generate the seven-membered palladacycle **32**, and subsequent reductive elimination would give the major isomer **21a**. In contrast, carbopalladation at the proximal double bond (as in eq 5 of Scheme 8 to form **25b**) would rationalize the formation of the minor isomer **21b**, with a steric effect in the carbopalladation of indolylpalladium(II) bromide allowing for the carbopalladation to proceed onto the proximal double bond, as depicted in **33**, to generate the η^3 -allylpalladium complex **34**. The second cyclization resulting from the sulfonamide group would then occur in an *anti*-manner to give the minor isomer **21b**. The formation of **21a** as the major product can be explained in terms of the strained bicyclic structure **33** in the carbopalladation step

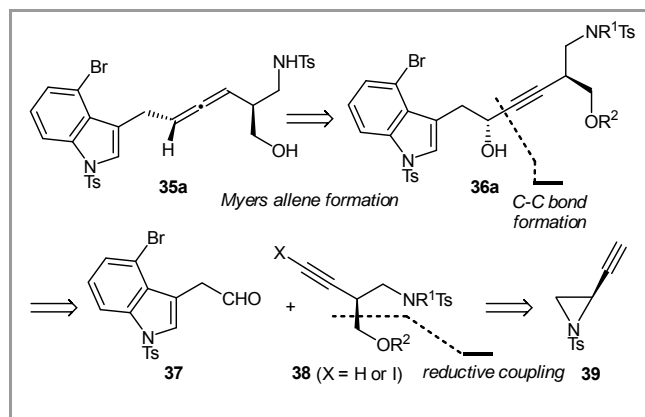


Scheme 9 Possible Pathways to **21a** and **21b** via Aminopalladation and Carbopalladation

2.2 Asymmetric Total Synthesis of (+)-Lysergic Acid and Related Alkaloids^{6d}

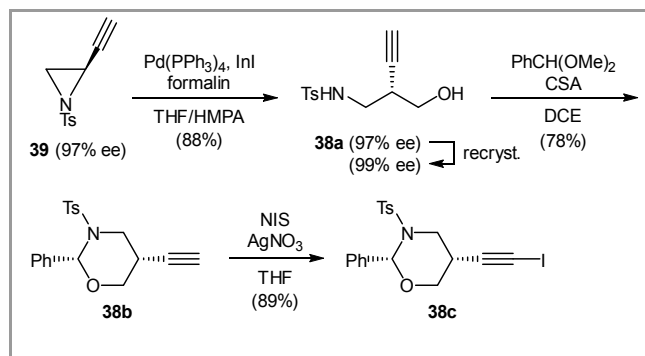
We then proceeded to investigate the asymmetric total synthesis of ergot alkaloids using the established cascade cyclization conditions for the construction of their core structure. In light of the difficulties that we experienced controlling the stereoselectivity of the Claisen rearrangement of propargyl enol ether **18** (Scheme 5), we made changes to the synthetic route used to access the amino allene. As shown in Scheme 10, it was envisaged that the chiral allene unit of **35a** could be constructed from enantiomerically enriched propargyl alcohol **36a** using the method reported by Myers.²¹ The propargyl alcohol **36a** could be obtained

from the coupling of aldehyde **37** with alkynes **38**. If necessary, oxidation and asymmetric hydrogenation reactions could be used for asymmetric induction at the propargyl position. The alkynes **38** could be accessed from the known 2-ethynylaziridine **39**,²² which can be derived from L-serine via an indium(I)-mediated reductive coupling reaction with formaldehyde, which was developed by our group.²³



Scheme 10 Retrosynthetic Analysis of Enantiomerically Enriched Cyclization Precursor **35a**

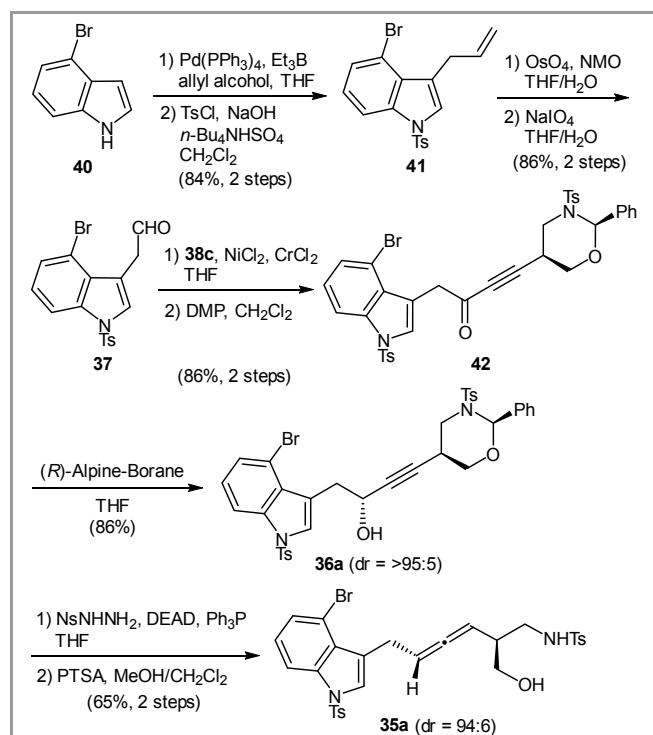
The synthesis of the alkynes **38** is shown in Scheme 11. Following our reported procedure,²² the enantiomerically enriched aziridine **39** (97% ee) was prepared from (*S*)-Garner's aldehyde²⁴ via sequential alkyne formation, deprotection, *N*-tosylation, and aziridine formation reactions. Treatment of the aziridine **39** with formalin under the InI-mediated reductive coupling condition [i.e., Pd(PPh₃)₄ (5 mol %), InI, THF/HMPA (4:1)]²³ gave the desired 1,3-amino alcohol **38a** (97% ee) in 88% yield. A single recrystallization afforded optically pure **38a** (99% ee). The benzylidene acetal **38b** and the corresponding iodoalkyne derivative **38c** were prepared by the treatment of **38a** with benzaldehyde dimethylacetal/CSA (followed by NIS/AgNO₃²⁵ for **38c**).



Scheme 11 Preparation of the Alkyne Units **38**. DCE = 1,2-dichloroethane

We next investigated the preparation of aldehyde **37** and its cross-coupling reaction with the alkynes **38**

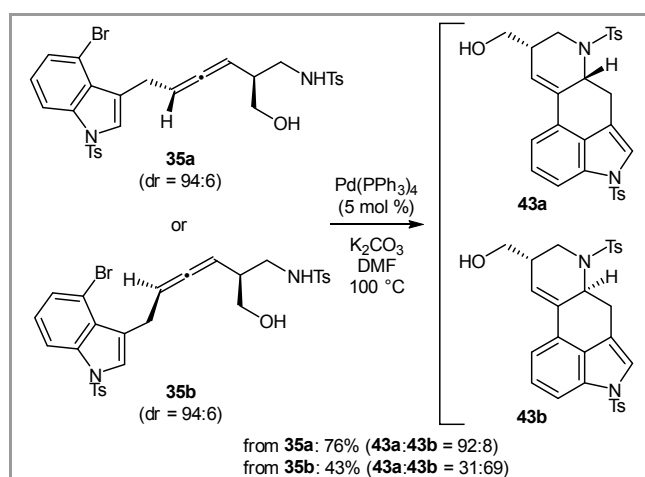
(Scheme 12). Commercially available 4-bromoindole **40** was converted to 3-allylindole **41** using a palladium-catalyzed C3-selective allylation reaction with allyl alcohol and triethylborane,²⁶ followed by *N*-protection. OsO₄/NaIO₄-mediated oxidation of **41** gave the desired aldehyde **37**. Among the different methods available for the coupling of **37** and **38**, including *n*-BuLi, *n*-BuLi/CeCl₃,²⁷ InBr₃/(*R*)-BINOL,²⁸ and Et₂Zn/(*S*)-BINOL/Ti(Oi-Pr)₄,²⁹ the Cr(II)/Ni(0)-mediated Nozaki-Hiyama-Kishi (NHK) reaction³⁰ using iodoalkyne **38c** was found to be the most efficient procedure, resulting in formation of the desired coupling product in 90% yield (dr = 1:1). Unfortunately, subsequent attempts to carry out the asymmetric NHK reaction³¹ failed to produce the desired propargyl alcohol, and an isomeric mixture of the propargyl alcohol was therefore oxidized to **42** and subjected to an (*R*)-Alpine-borane-mediated asymmetric reduction³² to afford the propargyl alcohol **36a** with high diastereoselectivity (dr = >95:5). Finally, the allenic amide **35a** was obtained from **36a** according to the method reported by Myers,²¹ with nosyl hydrazine being used under Mitsunobu conditions followed by the cleavage of the benzylidene group. The diastereomeric allenic amide **35b** (Scheme 13) was prepared in a similar manner via the reduction of ketone **42** with (*S*)-Alpine-borane.



Scheme 12 Stereoselective Synthesis of the Enantiomerically Enriched Cyclization Precursor **35a**. DMP = Dess–Martin periodinane.

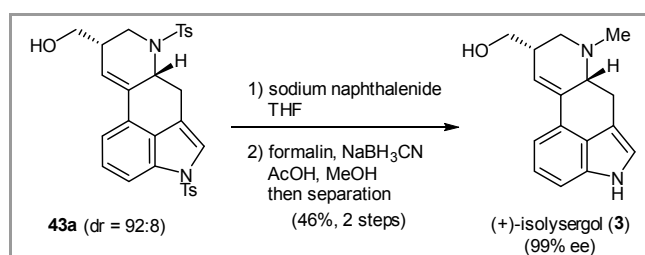
The construction of the ergot alkaloid skeleton via the palladium-catalyzed cascade cyclization of the allenic amides **35** bearing a free hydroxy group is shown in Scheme 13. The reaction of **35a** (94:6 isomeric

mixture) under the optimized conditions, which were developed above for the cascade cyclization of the racemic model substrates **19** and **20** bearing a silyl ether moiety (Scheme 6), provided the desired product **43** in 76% yield. The diastereomeric allenic amide **35b** afforded the cyclization products **43a** and **43b**, although the reaction was not as efficient or stereoselective (43% yield, **43a**:**43b** = 31:69). Once again, these results reveal the differences in the reactivity of the diastereomeric substrates.



Scheme 13 Cascade Cyclization of **35**

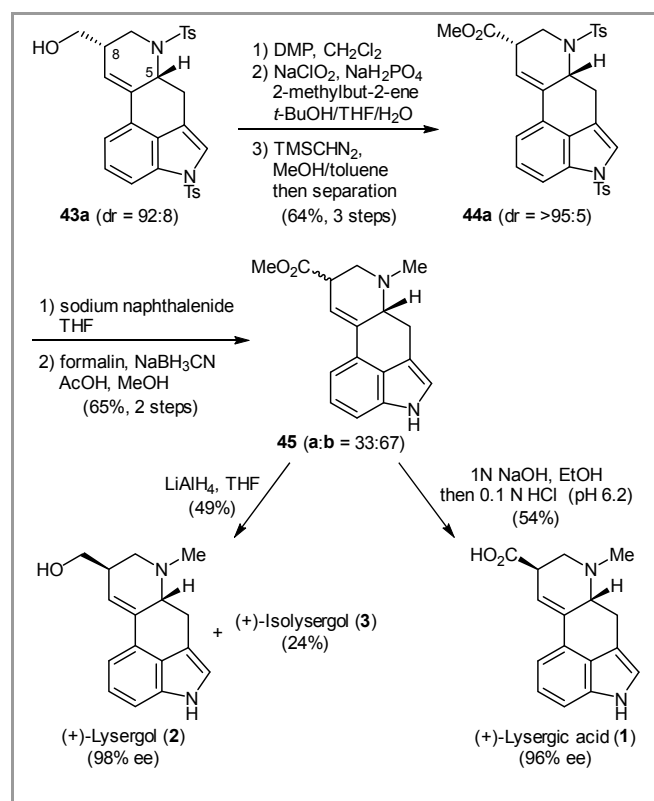
With the tetracyclic indole **43a** in hand with all of the requisite functionalities, we proceeded to investigate the total synthesis of the ergot alkaloids. A simple two-step procedure for the conversion of **43a** to isolysergol (**3**) is shown in Scheme 14. Removal of the tosyl groups of **43a** with sodium naphthalenide and subsequent *N*-methylation followed by separation of the diastereomers gave (+)-isolysergol (**3**) in 46% yield (99% ee, Chiralcel OD-H).



Scheme 14 Total Synthesis of (+)-Isolysergol (**3**)

The syntheses of lysergic acid and lysergol from **43a** would require the inversion of the stereochemistry at the 8-position, and this was accomplished by the epimerization of the corresponding ester derivatives (Scheme 15). Thus, the two-step oxidation of the primary alcohol in **43a** followed by esterification with TMSCHN₂ gave the corresponding methyl ester **44a** (64%, 3 steps). It was important to separate the diastereomers (derived from the chirality at the C-5 position) at this step for the preparation of lysergic

acid (**1**) and lysergol (**2**) in high ee, because the successful conversion of **44a** to **1** and **2** through isomerization would rely on the chiral information conveyed from the C-5 position. Cleavage of the two tosyl groups and subsequent reductive *N*-methylation led to a mixture of methyl isolysergate **45a** and lysergate **45b** (65% yield, **45a**:**45b** = 33:67). Reduction of this mixture with LiAlH₄ produced (+)-lysergol (**2**) in 49% yield (98% ee, Chiralcel OD-H), together with (+)-isolysergol (**3**) (24%).³³ Finally, the lysergate **45** (**45a**:**45b** = 33:67) was converted to (+)-lysergic acid (**1**) in 54% yield (96% ee, Chiralcel OD-H after methylation with TMSCHN₂)³⁴ by hydrolysis with NaOH with concomitant isomerization.^{6a} All of the spectroscopic data collected for the synthesized compounds **1**, **2**, and **3** were in agreement with those of the natural and synthetic products reported in the literature.^{6a,5c}



Scheme 15 Total Syntheses of (+)-Lysergic Acid (**1**) and (+)-Lysergol (**2**)

3 Quinocarcin Synthesis

(-)-Quinocarcin (**46**), which was originally isolated from the culture of *Streptomyces melanovineus*, is a pentacyclic tetrahydroisoquinoline alkaloid with antiproliferative activity against lymphocytic leukemia (Figure 2).³⁵ This particular compound is structurally similar to tetrazomine and lemonomycin, in that it shares a common skeleton composed of a piperizinohydro-isoquinoline motif. Saframycin and ecteinascidin 743 (Et-743, Yondelis®) differ in terms

of their D-ring, which is a six-membered ring.³⁶ Some of these compounds have been reported to display similar antitumor and antibiotic activities, with Et-743 in particular exhibiting high levels of activity towards a broad range of tumor cell lines at sub-nanomolar concentrations.³⁷ The development of a divergent synthetic route to this class of compounds would therefore be of considerable value for drug discovery.

The potent biological properties and challenging molecular architectures of these compounds have led to the development of several different creative approaches for their total syntheses.^{36,38-40} Most of the methods reported in this area, however, were designed for the specific synthesis of one of these compounds, with the Pictet–Spengler condensation reaction being used in the majority of cases for the construction of the isoquinoline core structure.^[38,39e,f,40] In the interest of developing a novel, general and convergent strategy capable of providing access to several different tetrahydroisoquinolines, we designed a unique method for the construction of the core structure of the tetrahydroisoquinoline alkaloids core using a Sonogashira-coupling/alkyne hydroamination sequence.

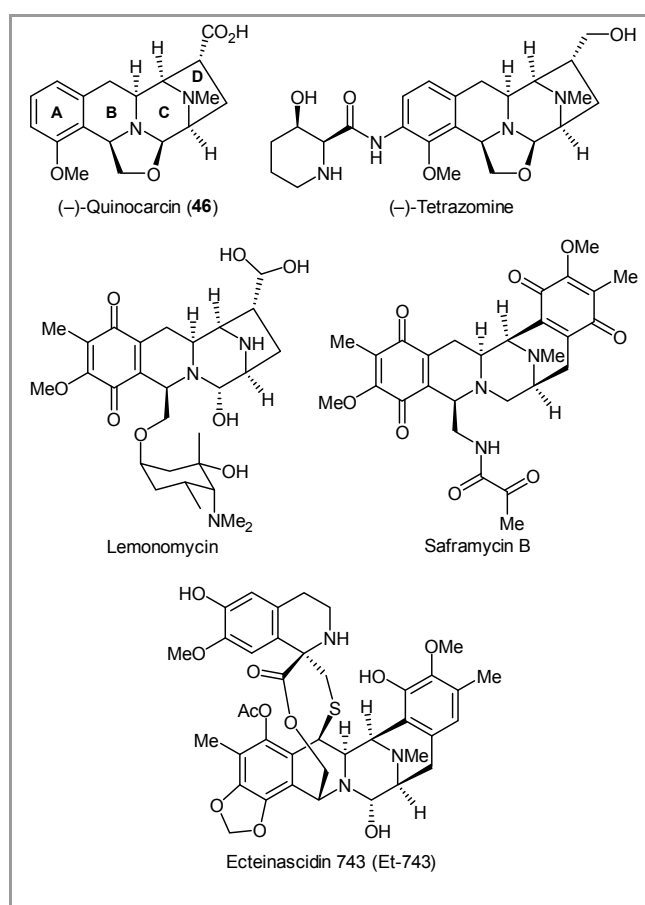
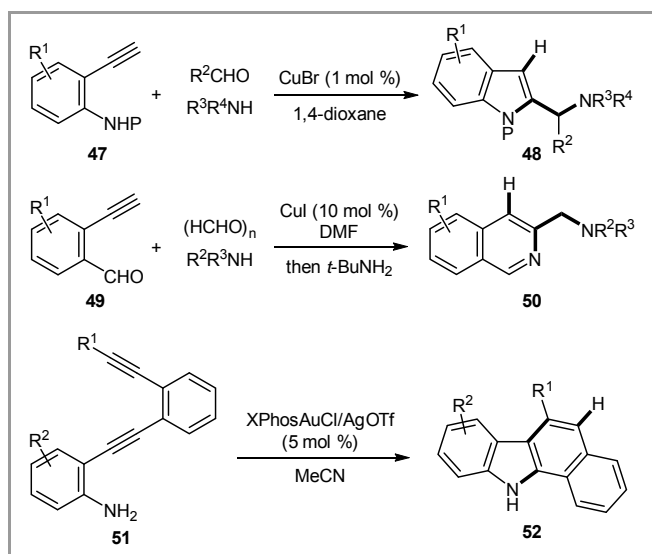


Figure 2 Quinocarcin and related tetrahydroisoquinoline alkaloids

3.1 Construction of the Core Structure by Gold-Catalyzed Alkyne Hydroamination^{39h,i}

Intramolecular alkyne hydroamination catalyzed by a transition metal complex provides atom-economical and straightforward access to nitrogen-containing heterocycles.⁴¹ Recent progress in homogeneous gold catalysis has revealed that cationic gold complexes are extremely useful for alkyne hydroamination reactions, which can afford the desired addition products under mild reaction conditions.⁴²

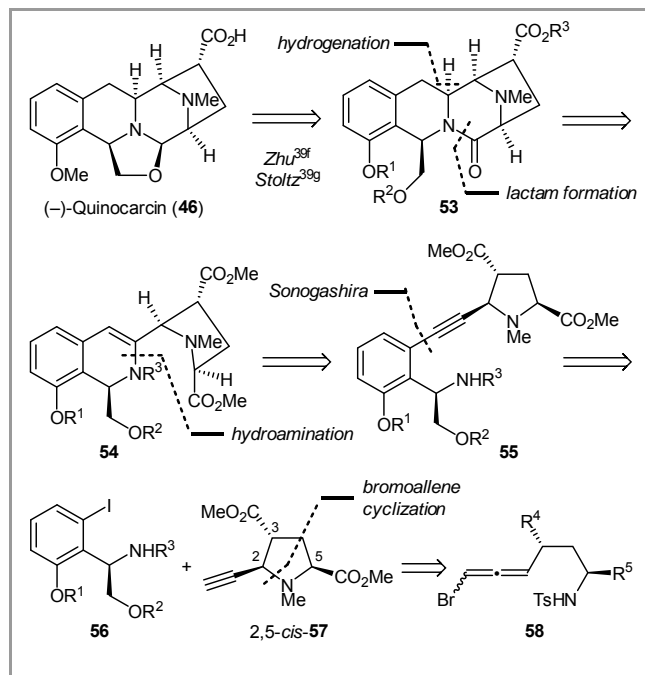
We recently reported the direct synthesis of 2-(aminomethyl)indoles **48** and related compounds via a copper-catalyzed three-component Mannich-type coupling reaction between protected 2-ethynylanilines **47**, aldehydes, and secondary amines followed by an intramolecular hydroamination (Scheme 16).⁴³ The use of 2-ethynylbenzaldehyde **49** as a starting material under these conditions provided access to isoquinolines.⁴⁴ We have also demonstrated that cationic gold catalysts promote the cascade cyclization of diynylaniline derivatives **51** to form fused carbazoles **52**.^{45,46} This transformation proceeded through an alkyne hydroamination reaction to form the indole ring followed by an alkyne hydroarylation.



Scheme 16 Transition-Metal-Catalyzed Alkyne Hydroamination Reported by Our Group

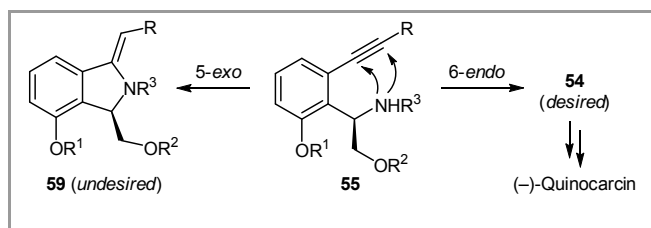
Based on these studies, we design a novel strategy aimed at providing access to the quinocarcin-type core structure through a transition-metal-catalyzed hydroamination. Our retrosynthetic analysis of (–)-quinocarcin (**46**) is shown in Scheme 17. It was envisaged that quinocarcin could be obtained from lactam **53** following the procedures reported by Zhu^{39f} and Stoltz.^{39g} This lactam could be synthesized via the hydrogenation of enamine **54** followed by an intramolecular amide formation. The enamine **54** could be accessed according to the intramolecular

hydroamination of alkyne **55**, which could be readily prepared by the Sonogashira coupling reaction of the iodinated phenylglycinol derivative **56** and 2-alkynylpyrrolidine **57**. It was also envisaged that the bromoallene cyclization reaction previously reported by our group⁴⁷ could be used for the stereocontrolled construction of the 2,5-*cis*-pyrrolidine **57**. This synthetic strategy was particularly attractive because different quinocarcin derivatives and other related alkaloids could potentially be obtained by simply changing the coupling components **56** and **57** during the latter stages of the synthesis.



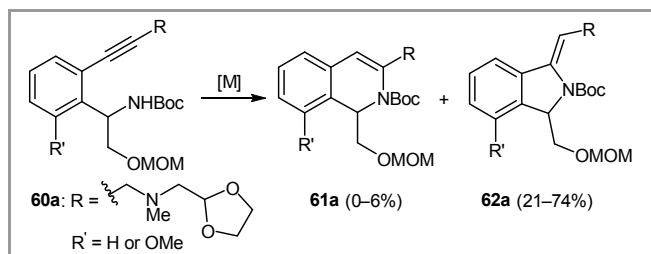
Scheme 17 Retrosynthetic Analysis of (–)-Quinocarcin

Control of the regioselectivity in the hydroamination of **55** would be critical to the success of this particular strategy. Thus, a 5-*exo-dig* cyclization would lead to the formation of the undesired isoindoline-type product **59** (Scheme 18), whereas a 6-*endo-dig* cyclization would afford the desired dihydroisoquinoline **54** required for the synthesis of quinocarcin. The 5-*exo-dig* cyclization could be predominated, however, because transition-metal-catalyzed C–N bond formation reactions generally occur at the more cationic carbon atom of activated alkynes bearing an aryl substituent. With this in mind, our initial work involved the use of a model study to accomplish the 6-*endo-dig* cyclization.

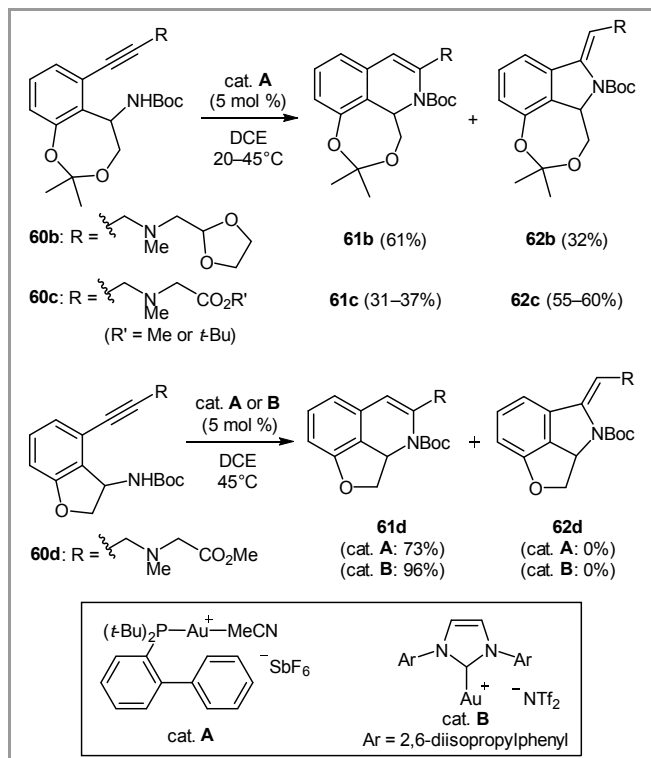


Scheme 18 Regioselectivity Issue in the Alkyne Hydroamination

The reaction of the model substrates **60a**, which was readily prepared by the Sonogashira coupling of the racemic aryl iodide with a propargyl amine, is shown in Scheme 19. Disappointingly, the hydroamination of **60a** using a variety of different transition-metal catalysts, including Au(I), Cu(I), Pt(II), In(III), and Rh(I) favored the 5-*exo-dig* cyclization in all cases to produce **62a**.



Scheme 19 Formation of the Undesired 5-*exo-dig* Cyclization Products



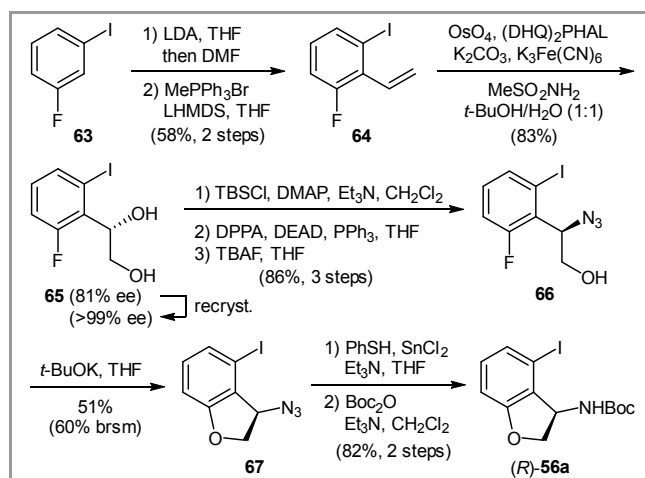
Scheme 20 Substrate-Controlled 6-*endo-dig* Hydroamination

The decision was then taken to modify the substrate structure (Scheme 20). Improvements in the regioselectivity were observed when the seven-

membered acetonide-type substrates **60b** and **60c** were treated with the gold catalyst **A**, with the desired 6-*endo-dig* products **61b** (61%) and **61c** (31–37%), respectively, being isolated in moderate yields. It was envisaged that the destabilization of the 5-*exo-dig* product would lead to further improvements in the regioselectivity. With this in mind, we proceeded to examine the reaction of dihydrobenzofuran-type substrate **60d**. In this particular case, the desired 6-*endo-dig* product **61d** was obtained exclusively in 73% yield. The gold catalyst **B** has proven to be highly active, affording **61d** in 96% yield. These model experiments therefore revealed that the phenylglycinol derivative **56** (Scheme 17) could be used as the target building block for the synthesis of quinocarcin as the corresponding dihydrobenzofuran-type aryl iodide.

3.2 Asymmetric Total Synthesis of (–)-Quinocarcin^{39h,i}

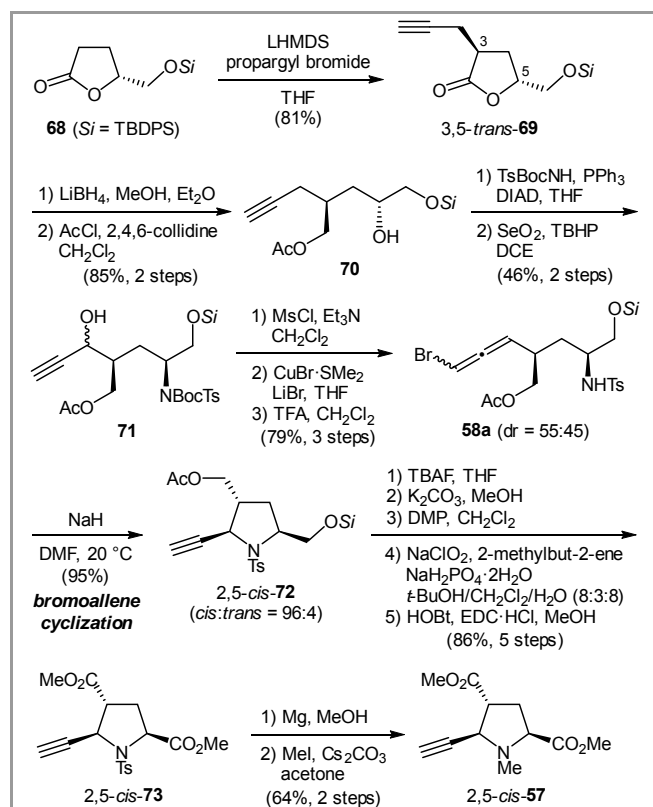
With an optimized procedure in hand for controlling the regioselectivity of the alkyne hydroamination reaction, we proceeded to investigate the preparation of the optically active dihydrobenzofuran (*R*)-**56a** (Scheme 21). Formylation of 3-fluoroiodobenzene **63** with LDA and DMF followed by the Wittig reaction of the resulting aldehyde afforded the dihalostyrene **64**. Subsequent Sharpless asymmetric dihydroxylation⁴⁸ of **64** and a single recrystallization provided the optically pure diol **65** (>99% ee), which was converted to the desired dihydrobenzofuran derivative (*R*)-**56a** via the introduction of an azide group with DPPA under Mitsunobu conditions,⁴⁹ followed by an intramolecular S_NAr reaction to form the dihydrofuran ring using *t*-BuOK, reduction of the azide group with PhSH, SnCl₂, and Et₃N,⁵⁰ and Boc protection.



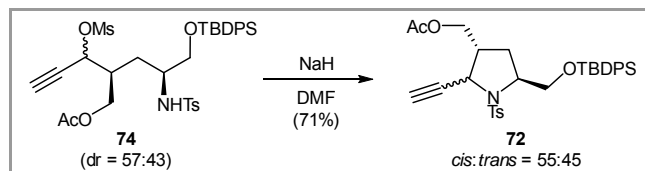
Scheme 21 Preparation of the Optically Active Dihydrobenzofuran (*R*)-**56a**. (DHQ)₂PHAL = hydroquinone 1,4-phthalazinediyl diether; DPPA = diphenylphosphoryl azide.

The preparation of the 2,5-*cis*-pyrrolidine **57** using the bromoallene cyclization is shown in Scheme 22. The

diastereoselective propargylation of γ -butyrolactone **68** gave the corresponding addition product **69**, which was reduced with LiBH_4 followed by selective acetylation of the primary hydroxy group to give alcohol **70**. Mitsunobu reaction with TsBocNH was then used to introduce the required nitrogen functionality, followed by selenium oxidation to give the propargyl alcohol **71** as a mixture of diastereomers. The bromoallene **58a** (dr = 55:45) was then formed using a standard protocol involving the sequential mesylation and bromination reactions with $\text{CuBr}\cdot\text{SMe}_2/\text{LiBr}$.⁵¹ As expected, the treatment of **58a** with NaH in DMF led to a stereoselective pyrrolidine formation to afford the desired 2,5-*cis*-**72** in 95% yield (2,5-*cis:trans* = 96:4). It is noteworthy that the intramolecular $\text{S}_{\text{N}}2$ reaction using mesylate **74** derived from **71** under identical reaction conditions afforded **72** as a mixture of diastereomers (2,5-*cis:trans* = 55:45) in a ratio corresponding to that of the mesylate **74** (Scheme 23). Thus, the mesylate-to-bromoallene conversion is important in terms of controlling the 2,5-*cis*-selectivity. The desired pyrrolidine **57** for the Sonogashira coupling was then prepared from 2,5-*cis*-**72** according to sequential oxidation, esterification, and *N*-methylation reactions using standard protocols.

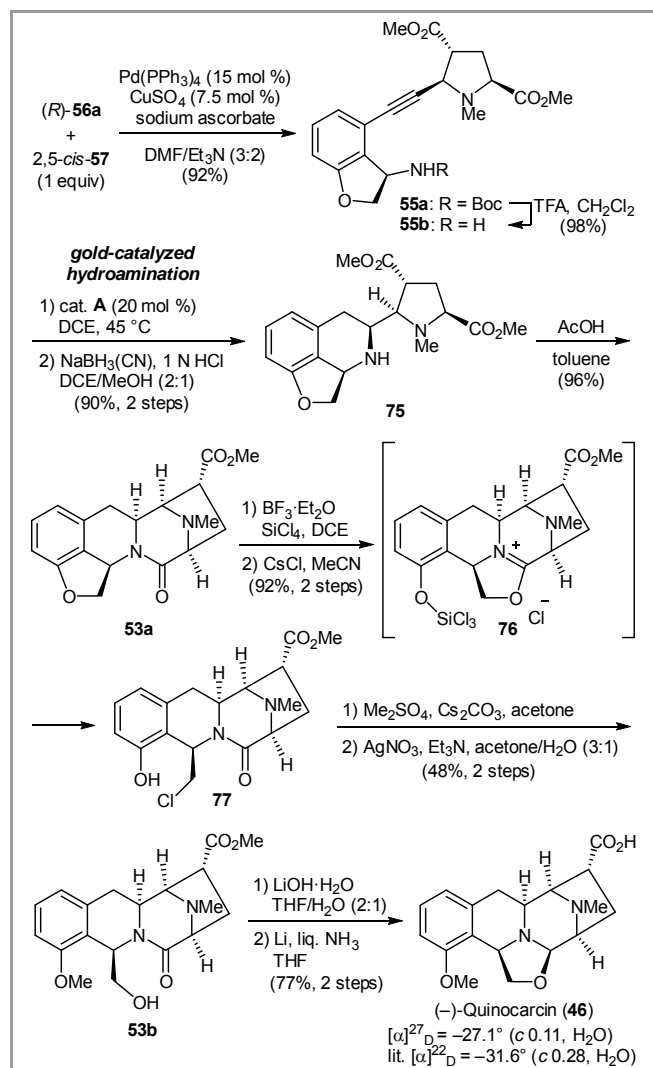


Scheme 22 Preparation of the Optically Active Pyrrolidine **57** via Bromoallene Cyclization. EDC = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide, HOBt = 1-hydroxybenzotriazole.



Scheme 23 Cyclization of Mesylate **74**.

We then moved on to investigate the coupling of the two building blocks (*R*)-**56a** and 2,5-*cis*-**57**, and the construction of the quinocarcin core structure (Scheme 24). The treatment of an equimolar mixture of the two components with $\text{Pd}(\text{PPh}_3)_4$, CuSO_4 , and sodium ascorbate⁵² gave the coupling product **55a** in 92% yield. Our initial attempt at the gold-catalyzed hydroamination using **55a**, however, was not as efficient, and gave the desired product in up to 46% yield using 40 mol% of cat. **A** (see Scheme 20). The lower yield observed in this case was attributed to unfavorable steric repulsion between the methyl ester at the C-5 position of the pyrrolidine and the *N*-Boc group in the conformer required for the hydroamination reaction. In contrast, the reaction of the corresponding amine **55b** proceeded more efficiently upon treatment with cat. **A**. Following the stereoselective reduction of the unstable hydroamination product with $\text{NaBH}_3(\text{CN})$, the tetrahydroisoquinoline **75** was isolated in 90% yield. As expected, the secondary amine selectively underwent lactam formation with one of the ester groups when **75** was heated in the presence of AcOH , leading to **53a** with the diazabicyclo[3.2.1]octane core structure in 96% yield.



Scheme 24 Total Synthesis of Quinocarcin

The remaining task of affecting the unusual dihydrobenzofuran cleavage required thorough investigation. Based on the ring-opening iodination reaction of dihydrobenzofuran with LiI in the presence of SiCl₄ and BF₃·AcOH reported by Zewge *et al.*,⁵³ we investigated the ring-opening reaction of **53a** assisted by the neighboring lactam carbonyl group.⁵⁴ It was envisaged that the treatment of lactam **53a** with the Lewis acids (in the absence of LiI) would afford the oxazolidinium intermediate **76**, which could be captured through an appropriate workup procedure. Unfortunately, however, the exposure of **53a** to BF₃·Et₂O and SiCl₄ in DCE followed by an aqueous workup of the resulting suspension (presumably containing **76**) only resulted in the recovery of the starting material **53a**. The failure of the reaction in this particular case was attributed to the hydrolysis of the transient silyl ether in **76** prior to the required cleavage of the oxazolidinium, which effectively promoted the reverse reaction from **76** to **53a**. Following a period of extensive experimentation using a variety of different Lewis acids, as well as investigating the capture of **76** through silane reduction and amidine formation, we found that the

addition of an excess of CsCl to the reaction mixture after the ring-opening reaction gave the chlorinated phenol **77** containing the quinocarcin core structure in 92% yield. Subsequent conversion of **77** to the known amide **53b** was achieved by the methylation of the phenol followed by hydrolysis of the carbon-chlorine bond in the presence of AgNO₃ and Et₃N. The total synthesis of quinocarcin was then completed using the procedure reported by Allan and Stoltz.^{39g} The spectroscopic data for our synthetic (–)-quinocarcin were identical to those reported.^{35,39}

3 Concluding Remarks

The work described herein demonstrates the enormous potential associated with the latest transition-metal catalyzed reactions for the synthesis of complex alkaloids. The highlights of the current work include the palladium-catalyzed cascade cyclization of allenes for the synthesis of ergot alkaloids and the gold(I)-catalyzed hydroamination of alkynes for the synthesis of the tetrahydroisoquinoline alkaloid, quinocarcin. These examples show that the use of transition-metal catalyzed reactions can provide a platform for the development of novel synthetic approach towards a range of different alkaloids, containing the important structural elements, and possibly lead to better synthetic access to alkaloid derivatives that would otherwise be difficult to obtain using conventional organic chemistry.

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Short Title: Syntheses of Alkaloids by Transition-Metal-Catalyzed Amination

